REMARKS/ARGUMENTS

Support for the amendment to claim 1 is provided at *e.g.*, p. 29, line 25. Support for the amendment to claim 3 is provided at *e.g.*, table 2, col. 2 at pp. 17-18. Applicants use the paragraph numbering of the office action in responding to the Examiner, comments.

¶¶16-18. No comment needed.

¶19. The Examiner alleges that applicant cannot use post-filing references to support enablement of the invention citing MPEP 2164.05(a). The Examiner therefore disregards Sigurdsson (2002) and (2003), cited as providing evidence that treatment of a mouse model of prion disease with PrP or an antibody thereto produces analogous results to those obtained on immunizing a model of Alzheimer's disease with Aβ or an antibody thereto.

In response, MPEP 2164.05(a) does not preclude submitting post-filing reference to support enablement. MPEP2164.05 reads in relevant part (italics supplied, underline in the original):

> Applicant should be encouraged to provide *any* evidence to demonstrate that the disclosure enables the claimed invention.....Once that evidence is submitted, it *must* be weighed with all other evidence according to the standards set forth above, so as to reach a determination as to whether the disclosure enables the claimed invention. To overcome a prima facie case of lack of enablement, applicant must demonstrate by argument and/or evidence that the disclosure, as filed, would have enabled the claimed invention for one skilled in the art at the time of filing. This does not preclude applicant from providing a declaration after the filing date which demonstrates that the claimed invention works.

The last sentence in the above excerpt illustrates a principle that evidence after the filing date can be relevant to confirm that the claimed invention works as described. The sentence expressly authorizes submission of a declaration, but does not exclude the submission of other forms of evidence that serve the same purpose of showing the claimed invention works as described. The preceding remarks of MPEP2164.05 encourage applicants to submit *any* evidence to demonstrate that the disclosure enables the claimed invention and require that such evidence *must be* considered.

Moreover, the Examiner has himself cited several post-filing references to attempt to show lack of enablement. It would be inequitable for the Examiner to pick and choose only those references he believes support his position, and dismiss without comment the references that do not.

The cited Sigurdsson's references speak for themselves in providing evidence that treatment of a mouse model of prion disease with PrP or an antibody thereto produces analogous results to those obtained on immunizing a model of Alzheimer's disease with Aβ or an antibody thereto. The authors acknowledge that their work represents an extension of previous work relating to Aβ immunization (*see Am. J. Pathol.* at p. 15, second column, first paragraph). No reason is apparent why evaluation of this evidence imposes greater difficulties than that of the other references cited by the Examiner. If some issue were in dispute regarding the interpretation of Sigurdsson's references, applicant would consider providing a declaration, but in the absence of such a dispute, it is submitted that the references should be considered based on their self-evident teachings.

¶20. The Examiner alleges there is no reasonable basis for extrapolating success in treating prion-based disease from treatment of Alzheimer's disease. Brown is cited as teaching that PrP and Aβ although similar exhibit fundamentally different neurotoxic effects on neurons. In response, the Examiner's comment are in part based on his ignoring the teaching of the Sigurdsson references as discussed above. Irrespective whether it was unpredictable *a priori* whether immunization with PrP would achieve analogous results to immunization with Aβ, the Sigurdsson references illustrate that such is the case. Similar results to those of Sigurdsson have been reported by others (*e.g.*, White, *Nature*, 422, 80-83 (copy attached)). The Examiner also does not take into account the parallel results between antibodies to Aβ and antibodies to synuclein discussed in the last response. Parallel results have also been reported for another amyloidogenic disease, Huntington's disease (*see* Miller et al., *Mol. Ther.*, 7:572-579). These results together with the data in the specification and those of Sigurdsson all support the view that amyloidogenic diseases are generally amenable to clearing on treatment with antibodies, whether delivered passively, or actively via immunization with an amyloidogenic peptide. The Examiner also does not take into the account the structural similarity of amyloid deposits in different amyloidogenic diseases discussed in the last response. Although it might be true that prions and Aβ exhibit different neurotoxicities on neurons, in each case the pathology results

from accumulation of structurally similar amyloid deposits. In each case, it would be expected that inhibition or clearing of deposits by antibodies would results in some beneficial effect on deleterious effects of the deposits even though the deleterious effects may vary between diseases.

¶21. The Examiner questions the relevance of *In re Brana* because no requirements for human testing have allegedly been set forth. Although no explicit requirement for human testing has been set forth, the Examiner has repeatedly speculated as to side effects that might be experienced by patients including side effects reported in a human clinical trial (*see* paragraph 19 of previous office action) and continues to do so in the present office action (*see* paragraph 17). *In re Brana* is relevant in establishing that the possibility of side effects is not inconsistent with enablement "Testing for full safety and effectiveness...is more properly left to the Food and Drug Administration (FDA). Title 35 does not demand that such testing occur within the confines of Patent and Trademark Office proceedings." *In re Brana,* 34 USPQ2d 1436, 1442 (Fed. Cir. 1995). *In re Brana* is also relevant in establishing that obtaining activity in an animal model is sufficient to satisfy the requirement of 112, first paragraph notwithstanding that the animal is not a perfect model of the human disease in every respect. Thus, insofar as the Examiner's allegations of nonenablement are based on the animals being imperfect models of Alzheimer's disease and prion disease in humans, or speculation as to possible side effects in humans, the position is in conflict with *In re Brana.*

¶22. The Examiner questions the relevance of *Nelson v. Bowler* on the basis that no question of pharmacological activity has been raised. In response, *Nelson v. Bowler* is relevant to enablement in that the utility of the invention determines what is needed to make or use the invention. *Nelson v. Bowler* establishes that a pharmacological activity in an animal model is sufficient for a composition to satisfy the utility standard. A specification need teach only a single use of a composition. Given that the Examiner agrees the claimed compounds have pharmacological activity in an animal model, it follows that the specification enables the compounds if the specification in combination with knowledge in the art teaches how to make and use the composition to achieve such a pharmacological activity. A pharmacological activity in an animal model is not inconsistent with the possibility of side effects. The Examiner's repeated allegations concerning possible side effects effectively impose a standard of enablement based on a different and more stringent utility than need be shown for a composition. The present compositions have a pharmacological activity in an animal model, and are enabled

because the specification teaches how to make and use the composition for that utility without undue experimentation.

¶23. The Examiner alleges that the specification does not provide any guidance or examples that would enable an artisan to make formulations containing prion proteins or to determine signs and symptoms of prion disorders to correlate with treatment. In response, the Examiner's has not addressed the considerable guidance provided by the specification at pp. 53-59 with respect to preparation of formulations for any amyloidogenic peptide, include PrP and AScr. A "specification disclosure which contains a teaching of the manner and process of making and using the invention in terms which correspond in scope to those used in describing and defining the subject matter sought to be patented must be taken as in compliance with the enabling requirement of the first paragraph of §112 unless there is reason to doubt the objective truth of the statements contained therein which must be relied on for enabling support." *In re Marzocchi*, 169 USPQ 367, 369 (CCPA 1971) (emphasis in original). Here, the Examiner has not met his burden of explaining why undue experimentation would be required to combine a prion protein with an adjuvant. With respect to sign and symptoms, it is noted that the present claims do not contain a monitoring step to detect such signs and symptoms. In any event, it is submitted that the signs and symptoms of prion-based diseases were well known in the medical field at the priority date of the invention (*see, e.g.*, Goldfarb, *Ann. Rev. Med.*, 46:57-65 (1995)) and do not require repetition in the application.

¶24. The Examiner again alleges difficulties in extrapolating from Aβ to prions. The Examiner also alleges there art-accepted animal models of PrP. The comments regarding extrapolating from Aβ to prion disease have been addressed above. Further, animal models of prion disease were available at the priority date of the claimed invention (*see e.g.*, Sigurdsson et al., *American J. Path.* 161, 13-17 (2002) citing to refs 13-15 from the 1980's as describing a "well-established model of prion disease at p. 14, first column, first paragraph, and Murammoto et al., *Nat. Med.*, 3, 750-5 (1997) describing an alternative transgenic mouse model).

¶25. The Examiner notes that there are a number of distinct prion-based diseases that share the common element of a prion protein but are caused by different mutations or isoforms. The Examiner takes the view that undue experimentation would be required as to how each individual isoform and mutation will affect the immune system of the patient. As discussed

above, the application discloses a general strategy in which pharmaceutical compositions comprising an agent and adjuvant generate an antibody response against an amyloid component and thus remove the amyloid component or reduce its further accumulation in amyloid deposits in a subject. This strategy accommodates different amyloidogenic diseases characterized by different amyloid components by appropriate selection of the agent in the composition. For example, to treat Alzheimer's disease, one can select an agent that generates an antibody response to Aβ, and to treat prion-based disease, one can select an agent that generates an antibody response to the prion component of the disease. Insofar as different prion-based diseases are characterized by different mutations or isoforms of prion protein, the different subtypes of disease can similarly be accommodated, if necessary, by selection of an agent that induces antibodies to the prion form present in the appropriate subtype. Mutagenic or isoform variation between different forms of prion-based disease does not, however, necessarily imply that a different agent is needed for treatment of each disease subtype. Although a particular mutation in a prion may be critically affect the path of disease, it is less likely to change substantially the immunoreactivity of the fragment. Thus, many antibodies against one form of prion protein are likely to react with other form notwithstanding mutagenic or isoform variation. For example, the antibodies shown to have pharmacological activity against prion-based disease by Sigurdsson *et al.*, *Neuroscience Letters*, 336, 185-187 (2003) were all raised against normal PrP rather than the pathogenic form, ASer. For these reasons, it is submitted that general strategy for design of pharmaceutical compositions can accommodate variations between prion protein in different types of prion-based disease.

¶26. The Examiner alleges additional unpredictability with respect to mutants, fragments, and peptides. The Examiner also says that for small peptides, conjugation appears to be required for promoting an effective immune response. In response, it is noted that the recitation of mutants, fragments and peptides occurred with respect to the description of a precursor protein in claim 3. Claim 3 has been amended to refer to mutations associated with hereditary amyloidosis. These are not random mutations, which may have the unpredictable effects, but rather natural mutations known to associated with amyloidogenic disease. There is no reason to think that immune responses directed to components derived from precursor proteins having such mutations would be less effective in treating prion disorders than immune responses directed to components from a wildtype precursor protein. With respect to the Examiner's comments on small peptides, the

specification teaches that such peptides are preferably conjugated to a carrier to improve the immune response (*see* specification at p. 44 *et seq*).

¶27. The Examiner alleges that general strategy of the application is insufficient because the examples are confined to the PDAPP mouse model and not prion disorders. The Examiner also alleges that the specification must establish that antigens injected into subjects produce a specific immune response without various side effects. The Examiner's first point raises the same issues discussed in paragraph (20) above. The Examiner's comments requiring the specification to teach achieving freedom from side effects impose too high a standard for enablement. As discussed above, it is sufficient that the specification discloses how to make and use the claimed compositions to achieve pharmacological activity in an animal model. The possibility of side effects is not inconsistent with a pharmacological activity.

¶28. The Examiner cited Wisniewski as teaching that use of a nontoxic form of amyloid protein is crucial for the success of any immune based therapies, and Tal as teaching that immunization with Freund's adjuvant alone has the same immunogenic effect as Freund's adjuvant with PrP. The Examiner now complains that applicant has not addressed any of the problems in the prior art or existing art. In response, it is submitted that neither reference is inconsistent with enablement. As pointed out in the last response, the results of Tal appear anomalous, and contrary to those of Sigurdsson *et al.*, *Am. J. Pathol.* 161, 13 (2002) in which immunization with prion protein and CFA significantly delayed onset of disease relative to immunization CFA alone. The parallel between treatment with Aβ or antibodies thereto and Alzheimer's disease, and prion protein or antibodies thereto and prion-based disease has been independently confirmed White, *Nature*, 422, 80-83 (2003). In any event, Tal's results tend to support rather than contradict the present specification's teaching that a composition of a prion protein and adjuvant has pharmacological activity in treating prion based disease. With respect to Wisniewski, in treatment of any disease, it can be acknowledged that the ideal therapeutic is one that is entirely free of toxicity. However, this ideal is rarely, if ever, realized and is certainly well beyond the requirements of enablement. As was discussed above, a pharmacological composition is enablement if the specification teaches how to obtain a pharmacological activity using the composition. Neither reference provides any reason to doubt that a composition of prion protein plus adjuvant would have pharmacological activity in an animal model. The

citation of the references does not satisfy the Examiner's burden of proof in establishing lack of enablement.

¶29. In the previous response, applicant pointed out that certain references allegedly teaching that prion protein may cause a prion disorder rather than alleviate it administered prion protein without an adjuvant or otherwise under conditions not calculated to generate antibodies. Applicant also pointed out that the use of an adjuvant, as recited in the presently claimed composition, favors the desired beneficial response. The Examiner now states that applicant's statement was made in the absence of evidence. The Examiner also cites Harmeyer as teaching that immunization of mice with 16 synthetic peptides derived from PrP yields monoclonal antibodies which vary in their specificity, strength of binding and Ig class, from which the Examiner alleges undue experimentation would be required to achieve the desired effects.

With respect to Examiner's allegations regarding lack of evidence, it is noted that applicant has supplied a reference (*i.e.*, Sigurdsson, *Neuroscience Letters*, 336:185-187 (2003)) in which administration of prion protein plus adjuvant did achieve a therapeutic effect. It is submitted that this evidence, in which a prion protein was administered with an adjuvant is more pertinent than the Examiner's references, in which prion protein was submitted without an adjuvant and is thus outside the claim scope. Even if the evidence were in "equipoise," an inventor is "entitled to a patent." *In re Oetiker*, 24 USPQ2d 1443, 1447 (Fed. Cir. 1992) (Plager, J., concurring).

With respect to the second point, the Examiner appears to assume that a particular epitope specificity is required for a therapeutic effect. However, Sigurdsson administered three different monoclonals with three different epitope specificities, each of which achieved a therapeutic effect. Thus, it appears that multiple specificities can be used. In any event, appropriate specificities can be determined by repetition of the same assay in the same animal model. In many instances, results from testing one fragment can be used to predict other fragments that are likely to be successful. For example, if a particular fragment is effective, larger polypeptides including the fragment are also likely to be successful. Conversely, if a particular fragment is not effective, subfragments are not likely to be effective either. Thus, a reasonable number of effective fragments can be determined by routine repetition of the same procedure. Routine repetition does not constitute undue experimentation. Finally, the

Examiner's comments concerning a need to experiment whether an adjuvant is required are incorrect, because the claims require an adjuvant.

¶30. The Examiner cites Goldsby as teaching that active immunization is not predictable as peptides are not generally immunogenic. In fact, Goldsby does not say that peptides are not generally immunogenic but only that they are not *as* immunogenic as proteins (p. 461, second column, first paragraph). In any event, peptides can be made immunogenic using a carrier. The Examiner cites Diomede as discussing possible toxicities of prion protein to certain types of cells *in vitro*. In response, it is submitted that the relevance, if any, of these in vitro observations to in vivo administration is speculation. In any event, applicant reiterates that enablement of the present methods does not require freedom from all side effects.

¶¶32-33. Claims 1-8 and 10 stand rejected under 35 U.S.C. § 112, first paragraph for alleged lack of written description. The Examiner alleges that the claims do not require the agent to possess any particular conserved structure or distinguishing feature. The Examiner also alleges that applicant has admitted on the record that "no known agent was in fact in the possession of the inventors at the time of filing." The Examiner cites University of Rochester vs. Searle as being allegedly analogous to the present situation. The Examiner notes that no actual agent was identified in the Rochester case. Applicant respectfully traverses.

First, applicant has not admitted on the record that "no known agent was in fact in the possession of the inventors at the time of filing." The Examiner has attributed words to applicant that were never said. To the contrary, as discussed below, applicant was in possession of known agents suitable for use in the claimed methods at the time of filing.

The criterion for possession is not a literal test of whether applicant physically had a compound in his custody at the date of filing the patent application. Rather, possession is a legal concept satisfied when an applicant discloses any combination of identifying characteristics that distinguished the claimed invention from other materials. *Regents of the University of California v. Eli Lilly*, 43 USPQ2d 1398, 1406 (Fed. Cir. 1997). Here, particularly as amended, the claims do identify sufficient characteristics to distinguish the claimed methods and the compounds used in them from other methods and compounds. The claims as amended are directed to methods in which the agent administered is an amyloidogenic protein or a fragment thereof. Amyloidogenic proteins include many well-characterized proteins whose sequences were available from the scientific literature at the effective date of the application. Exemplary

citations to the scientific literature are provided in the specification. Anyone can visualize numerous known amyloidogenic proteins, including prion protein, or any fragment thereof. Thus, applicant was in possession of amyloidogenic proteins and their fragments at the effective filing date of the application.

The present facts and circumstances are distinct from those of *University of Rochester vs. Searle*. In the Rochester case, as the Examiner has said, there were no known compounds that could be used in the claimed methods. The methods were thus described only by a result sought to be achieved, and could not necessarily be distinguished from other methods. Here, the specification provides data showing inter alia that Aβ can be used in treatment of Alzheimer's disease and disclosure that other members of the same class of well-characterized compounds (*i.e.*, amyloidogenic proteins) can be used in treating corresponding diseases associated with amyloid deposits. The methods are thus described not only by the result to be achieved but by reference to a known class of proteins to be used as therapeutic agents. By described his claimed invention in a way that distinguishes it from other methods, applicant has shown possession of it.

If the Examiner believes a telephone conference would expedite prosecution of this application, please telephone the undersigned at 650-326-2400.

Respectfully submitted,

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